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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/463,590	04/20/2000	SAMUEL J. LANDRY	07005/00302	6521

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KRISTINA BIEKER BRADY
CLARK & ELBING
176 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
DECLOUX, AMY M	
ART UNIT	PAPER NUMBER
1644	10

DATE MAILED: 05.07.2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/463,590	LANDRY, SAMUEL J.	
	Examiner	Art Unit	
	Amy M. DeCloux	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-13,15-19 and 58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-13,15-19 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 April 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's amendment filed 1-28-02 is acknowledged and has been entered.

In view of applicant's amendment, the outstanding objections have been withdrawn. However the written description and enablement rejections have been maintained, though modified, and applied to all pending claims. Also the enablement rejection applied to Claim 58 has been maintained. Also a new art rejection has been applied to claims 1, 15 and 18.

Accordingly, this office action is nonfinal.

2. Formal drawings and/or photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the PTO-948 form attached to the office action mailed 9/25/01 (Paper No.8).

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

A). Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B) Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of
informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDONMENT of the application.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. MAINTAINED Claim 58 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 58 recites a method for stimulating an immune response toward a naturally occurring HIV GP120 protein comprising administering an altered HIV gp120 protein wherein a human HSP mobile loop has been inserted by artifice into said altered HIV gp120 protein. There is insufficient guidance and direction regarding the sequence and structure of the human HSP-10 mobile loop inserted into the HIV gp120 protein. Therefore one of skill in the art would not know how to make said recited altered HIV gp120 protein and accordingly there is insufficient guidance and direction in the instant specification on how to practice the claimed method. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Based upon said insufficient guidance in the instant specification, it would require an undue amount of experimentation on the part of one skilled in the art to use the claimed altered gp120 polypeptide in the recited method of stimulating the immune response against a naturally occurring HIV GP120 protein.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Response to Arguments

Applicant's arguments filed 1-28-02 have been fully considered but they are not persuasive. Applicants contend that the mobile loop of HSP10 is a specific example of an unstable polypeptide segment as defined by the specification. However, the examiner notes that though the specification discloses the mobile loop of HSP10 of M. leprae in Figure 1, the specification does not disclose what the mobile loop of human HSP recited in claim 28 is.

4. MAINTAINED Claims 1-8, 10-13 and 15-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

In the instant case, the specification does not convey to the artisan that the applicant had possession, at the time of invention, of the claimed unstable polypeptide sequence (with the exception of the unstable polypeptide segment of the mobile loop of HSP10) comprised by a method for stimulating an immune response specific toward a naturally occurring protein as recited in Claims 1-8, 10-13 and 15-19. The instant claims merely recite said sequence in terms of several properties (unstable,

hydrophobicity, sequence conservation, amide protection factor, NMR order parameter and average B-factor parameter) but exemplifies only one such unstable polypeptide (the unstable polypeptide segment of the mobile loop of HSP10) . Due to this broad number of polypeptides encompassed by the genus of unstable polypeptide segments, the disclosure of one species provides insufficient written description of the claimed genus. Therefore, the instant claims fail to meet the written description provision of 35 USC 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See Vas-Cath, page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath, page 1116.).

The skilled artisan cannot envision all the unstable polypeptide sequences (with the exception of the unstable polypeptide segment of the mobile loop of HSP10) that could be inserted by artifice in the recited altered protein, and therefore conception cannot be not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

Response to Arguments

Applicant contend that by amending the base claim to contain the limitations of claim 9 and claim 14, as suggested by the examiner, they will have overcome the rejection. Hoewever, the examiner upon further consideration, for the reasons discussed above in the modified rejection, has found that adding said limitations is not sufficient.

5. MAINTAINED Claims 1-8, 10-13 and 15-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for stimulating an immune response specific toward a naturally occurring protein comprising administering an altered protein or polypeptide fragment thereof derived from said naturally occurring protein, wherein an unstable polypeptide segment has been inserted by artifice into said altered protein, wherein the unstable polypeptide segment is the mobile loop of HSP10, does not reasonably provide enablement for the broader recitation of a method for stimulating an immune response specific toward a naturally occurring protein comprising administering altered protein or polypeptide fragment thereof derived from said naturally occurring protein, wherein any unstable polypeptide segment has been inserted by artifice into said altered protein, and/or wherein immunogenicity of the naturally occurring protein is not increased. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed in claims 1-8, 10-13 and 15-19 without an undue amount of experimentation. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the large number of unstable polypeptide segments, known and unknown, broadly encompassed by the claims.

The instant specification provides insufficient guidance for a method encompassing any unstable polypeptide segment other than wherein the unstable polypeptide segment is the mobile loop of HSP10. It is known in the art that even a single amino acid change or difference in a protein's amino acid sequence can have dramatic effects on the protein's function, as evidenced by the teachings of Abaza et al (J. Of Protein Chemistry, 11(5):433-444, 1992). Abaza et al show that even a single amino acid difference in an antigen may effect antibody binding by teaching that an amino acid substitution of myoglobin outside the epitope recognized by a monoclonal antibody causes the myoglobin to be unreactive with said antibody, (see entire article, especially the Abstract). Further Hubbard et al (IDS) teach in Protein Science (1994) that specific conformations are required for cleavage of limited proteolytic sites to enable the protease to bind and cut (see entire article including the Abstract). Since antigenic epitopes are generated through proteolysis in the cell, a proper conformation must be achieved in the protein for proteolysis, and therefore inserting any instable segment may not lead to a proper conformation for proteolyis by endogenous proteases. Therefore predicting which unstable polypeptide segment other than that wherein the unstable polypeptide segment is the mobile loop of HSP10, that is

effective in providing a proteolytic site in a naturally occurring protein which will stimulate an immune response presumably by generating peptide fragments for presentation by MHC molecules, would require undue experimentation.

In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention and this is not sanctioned by the statute.

Response to Arguments

Applicant contend that by amending the base claim to contain the limitations of claim 9 and claim 14, as suggested by the examiner, they will have overcome the rejection. Hoewever, the examiner upon further consideration, for the reasons discussed above in the modified rejection, has found that adding said limitations is not sufficient.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6.NEW Claims 1, 15 and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Knuth et al. (US Patent 5, 989,554)

'554 teaches a method of inserting a protein into a ligand, wherein said protein is non-naturally occurring and wherein at least 95 % of the amino acids are selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, serine, threonine, proline, glutamine, asparagine, phenylalanine, tyrosine and histidine, and wherein said ligand does not require the use of an adjuvant to elicit an immune response to the ligand when the ligand is fused to said protein, when administered (see entire patent, especially claims 1 –5 and columns 3-4). It is noted that the referenced claims do not teach all the limitations of the instant claims; however, due to the hydrophobicity of the inserted protein, the recited properties would be reasonably expected. The burden is on the applicant to establish a patentable distinction between the claimed and referenced altered proteins and the methods stimulate an immune response using said altered proteins. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy M. DeCloux whose telephone number is 703 306-5821. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 703 308-3973. The fax phone numbers for the organization where this application or proceeding is assigned are 703 305-3014 for regular communications and 703 305-7401 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308-0196.

David A Saunders

DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT ~~182~~ 1644

Amy DeCloux, PhD
Patent examiner, 1644
May 6, 2002